REMARKS

Claims 1, 3-4, 8-11, 13-24, 26-28, 30, 33-37, and 46-48 are under examination. Claims 2, 12, 25, 31 and 32 are canceled by this amendment. The pending claims have been amended to more particularly specify the claimed subject matter. No new matter has been added. Reconsideration is requested.

Rejections Under 35 USC §102

Claims 1-4, 8, 10, 12-17, 19-21, 26-29, 31-37 and 46-48 were rejected under 35 USC § 102(b) as being anticipated by Bab et al. (WO 95/00166). This rejection is traversed for the following reasons.

The Examiner indicates that Bab et al. teach administering YGFGG in phosphate buffered saline (PBS) to mice once a day for twelve days, on day 8, mice were treated with a single X-ray radiation and on day 14, mice were sacrificed and their bone marrow was isolated and analyzed. The Examiner further indicates that administration of this peptide stimulated the production of bone marrow cells (page 14, line 29, through page 15, line 5).

The Examiner further states that the discovery of a new use for an old structure might be patentable as a process of using, but that when the claims recite using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated.

The Examiner further indicates that while Bab et al. do not teach all the effects recited in claims 1, 8, 13, 15, 19, 25, 26, 28, 29, 30, 37, 46 and 48, they do perform the same administration of this peptide as in the present application (Examples 1, 3 and 4), and therefore inherently teach the same effects as those recited in claims 1, 8, 13, 15, 19, 25, 26, 28, 29, 30, 37, 46 and 48.

Regarding claims 2, 3, 12, 14, 27, 31-36 and 47, the Examiner asserts that these dependent claims do not further limit the steps recited within their respective independent claims *per se*, but rather describe the effects of the steps. Therefore, it is his position that these claims are also anticipated by the Bab et al. reference.

Still further, the Examiner alleges that claims 19, 25, 26 and 29 (which has been previously canceled) require "exposing" cells to YGFGG, which is anticipated by the administration to mice taught by Bab et al. The Examiner particularly indicates that the term "exposing" dose not particularly limit the manner in which the cells and the peptide interact. The Examiner further indicates that the term "exposing" does not require, for example, that the cells be cultured *in vitro* and contacted directly with YGFGG peptide. Claims 19 and 26 have been amended to be limited to "*in vitro*" exposure of the cells (please note that claims 25 and 29 have been canceled), and are therefore believed to be free of the rejection.

The Examiner further asserts that claims 9 and 30 require that the subject be undergoing irradiation, and in day 8 of the method of Bab et al., mice were irradiated and injected with the peptide. The claims have been amended to be limited to subjects undergoing chemotherapy or suffering from a hematological disorder, and are believed to be free of the rejection.

Claims 20 and 21 require that the subject be suffering from hematological disorder. The Examiner contends that this aspect is anticipated by the irradiated mice displaying low number of bone marrow cells as described by Bab el al. (page 15). These claims have been restricted to include the chemotherapy and mobilization elements, which are not disclosed in Bab et al. Accordingly, they are submitted to be free of the rejection. Reconsideration and withdrawal thereof are respectfully requested.

Regarding claim 28, the Examiner indicated that this claim requires obtaining "a sufficient amount" of stem cells from the treated subject, but since the claim does not particularly define any criteria for including a particular number of cells and excluding another or a requirement that the stem cells be purified to homogeneity, this claim is anticipated by the bone marrow isolation of Bab et al.

The Examiner states that arguments filed in response to the previous Office Action have been fully considered, but they are not persuasive. The Examiner specifically indicates that in this case, Bab et al. teaches exactly the same steps as those claimed by the applicant, *i.e.* the administration of the YGFGG oligopeptide to patients receiving irradiation (the Examiner specifically refers as an example, to claim 1, which allows that the patient may be receiving irradiation but not necessarily chemotherapy). The Examiner concludes therefore that in this case, the patient set (i.e., subjects receiving irradiation) and the administration step (i.e., administration of YGFGG oligopeptide) taught in Bab are identical to the patient set and administration step as claimed; therefore, all outcomes of this administration step on the patient set are inherent outcomes, whether or not they were recognized by Bab at the time. The Examiner states that an amendment of the claims to distinguish their patient set or administration step from that of Bab et al, might overcome this ground of rejection.

In order to further distinguish the present claims from Bab et al., they have been restricted to subjects receiving chemotherapy and suffering of hematological disorders. These limitations are not disclosed or suggested by Bab et al. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner further contends regarding applicant's allegation that Bab does not teach mobilizing a particular subset of cells, that the claims are not so limiting. The Examiner states that all that is required in the claims is that "multilineage hematopoietic stem cells" with particular markers (claims 1-3), "early CD34-positive stem cells" (claim 8), "CD34 positive hematopoietic stem cells" with particular markers (claims 13-14), "BFU-E and GFMM CFUs" (claims 15 and 19), "hematopoietic CD34 positive cell stem cells" (claim 26), "hematopoietic stem cells" (claim 28), "circulating stem cells" (claim 30), and "circulating hematopoietic stem cells" (claim 48). Claims 21, 23, 37, and 46 merely require "treating" and does not recite any cell mobilization at all. Furthermore, the methods "comprise" the administration of YGFGG and therefore do not rule out the inclusion of additional administration steps that might mobilize other cell types. The Examiner further concludes that applicant is arguing limitations not recited in the claims. In response, the method claims have been limited to "method consisting of the step of" as suggested by the Examiner (e.g. claims 1, 13, 15, 19, 20, 23 and 26), and the mobilization aspect has been added as appropriate (e.g. claims 8, 20 and 23 for example).

For all of the above reasons, it is respectfully submitted that presently amended claims 1, 3-4, 8-10, 12-17, 19-21, 25-37 and 46-48 are not anticipated by Bab et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 19, 26-28 and 46-48 remain rejected under 35 USC § 102(a) as being anticipated by Chen et al. (2000, Journal of Peptide Research 56: 147-156). The Examiner particularly referred to page 155, column 1 of this reference asserting that Chen et al., teach administering YGFGG (OGP(10-14) in phosphate buffered saline (PBS) to mice. It is the Examiner's position that claims 27 and 47 do not further limit the steps recited within their respective independent claims *per se*, but

rather describe the effects of the steps, and that accordingly these claims are also anticipated by Chen et al. Furthermore, the Examiner alleged that claims 19 and 26 which require "exposing" cells to YGFGG, are anticipated by the administration to mice taught by Bab et al. The Examiner particularly indicated that the term "exposing" does not limit the manner in which the cells and the peptide interact. The Examiner noted that the term "exposing" does not require, for example, that the cells be cultured *in vitro* and contacted directly with YGFGG peptide. The Examiner further clarifies that this rejection is maintained only over claims 19, 26-28 and 46-48, indicating that none of these claims requires that the method be performed on a subject undergoing radiation, chemotherapy, or transplantation or on subject suffering from a hematological disorder.

In order to advance prosecution, claims related to methods of treatment have been limited to patients receiving chemotherapy and suffering of hematological disorders (claims 28, 46-48), and claims 19 and 26-27 have been restricted to "*in vitro*" methods (wherein "exposing" said cell is performed *in vitro*). It is respectfully submitted that the amended claims are free of this rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner further cited Gurevitch et al. (1996, Blood 88: 4719-4724) taken in the light of Bab et al. (1999, Journal of Peptide Research 54; 408-414) as anticipating claim 19 under 35 U.S.C. 102(b). The Examiner specifically referred to the "comprising" language of this claim. In response, the term "comprising" has been amended to "consisting of" in said claim. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 8, 11, 15, 18, 20 and 22-24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bab et al. (WO 9500166A) taken in view of Takayama et al. (1999, U.S. Patent 5, 910, 303). The Examiner indicated that Bab et al. do not teach treatment of myeloproliferative

disorders or specific increase of circulating CD34+ stem cells or CFUs in subject with myeloproliferative disorder. It is the Examiner's view that Takayama et al. teach treating myeloproliferative disorders, including myelofibrosis, with an agent that promote platelet and leukocyte production and reversing the damage to bone marrow caused by irradiation therapy (column 12, Examples 1 and 2). The Examiner believes that a skilled artisan would have had a reasonable expectation of success in treating myeloproliferative disorders including MF, with the pentapeptide of Bab et al., which teaches that this peptide stimulates bone marrow cell production and subsequent repopulation of immune system. It is respectfully submitted that as indicated in our previous response, the OGP(10-14) pentapeptide was clearly shown by the invention as exhibiting a specific growth enhancing effect on certain lineage of circulating early stem cells ($CD34^+$). It should be stressed that CD34 antigen is present only in approximately 2-3% of the human bone marrow cells, specifically in early myeloid cells that express the CD33 antigen but lack the CD14 and CD15 antigens and in early erythroid cells that express the CD71 antigen and dimly express the CD45 antigen, and in all hematopoietic colony-forming cells in bone marrow and blood, including unipotent (CFU-GM, BFU-E) and pluripotent progenitors (CFU-GEMM, CFU-Mix, and CFU-Blast). Please note that normal peripheral blood lymphocytes, monocytes, granulocytes, and platelets do not express the CD34 antigen (emphasis added).

The present invention further shows that OGP(10-14) pentapeptide specifically enhances the growth of the pluripotent progenitors CFU-GEMM [these progenitors may differentiate into BFU-E (which differentiate into Red blood cells), CFU-Meg (as shown by Figure of **Exhibit A** (submitted in the last response)), these progenitors can differentiate into the megakaryocytes and macrophages), to CFU-GM (that differentiate into neutrophil and monocytes which are the precursors of macrophage

(are also particular leukocytes)) and to CFU-Eo (that can differentiate into eosinophils and basophils, which are also particular leukocytes)].

Moreover, further progenitor cell assay shown in Example 3 of the present application (page 45), indicates that this OGP(10-14) pentapeptide increases the BFU-E unipotent cells that differentiate into erythrocytes, but not CFU-GM (that differentiate into neutrophil and monocytes which are the precursors of macrophage).

Thus, as surprisingly shown by the present invention, the OGP(10-14) peptapeptide demonstrates specific growth effect on a particular pluripotent myeloid (and not lymphoid) early $CD34^+$ stem cells, and more particularly, on circulating stem cells, the BFU-E. These particular properties of the peptide firstly disclosed by the invention enable the use of this peptide in methods of treatment of particular hematological disorders and particularly of myeloid disorders, such as IMF.

It is therefore emphasized that the OGP(10-14) peptapeptide of the invention would not affect platelets or leukocytes. In contrast, as also indicated in our previous response, the Takayama patent demonstrates that IFNγ in itself induces the reduction of the platelet level in mice, but strongly augments the activity of promoting the platelet production (emphasis added) of biologically active substance such as IL-3 (see column 7, last paragraph). Moreover, all eight figures of this patent describe the effect of combination of IFNγ and IL-3 on thrombocytopenia ((decrease in the number of platelates) and leucopenia (decrease in the number of circulating white blood cells (leukocytes) in the blood). The Examples referred to by the Examiner are only illustrative and indicate the preparation of an agent comprising IFNγ and IL-3 (Example 1, column 12) and IFNγ and GM-CSF (Example 2, column 12), for the treatment of a variety of diseases including myelofibrosis. Therefore, the Examiner's statement that "treatment with an agent that promotes platelets and leukocyte production"

would be expected by the skilled artisan as relevant to myeloproliferative disorders such as IMF, is not correct, since although relevant to leucopenia and thrombocytopenia, such a substance (promoting platelets and leukocyte production) cannot be relevant to variety of diseases including myelofibrosis. Thus, if anything, this patent teaches only the combination of IFNγ with another known "substance" and particularly, IL-3, for treatment of thrombocytopenia and leucopenia. This would not motivate the skilled artisan necessarily to use the pentapeptide of Bab et al, which was firstly shown by the present invention as relevant to myeloproliferative disorders. This novel application of a known compound was revealed by the present invention through the discovery of the unique and novel effect of this pentapeptide on CD34 positive cells and particularly on BFU-E, which are applicable in treatment of such disorders.

Therefore, this patent by itself, or in combination with any of the references cited by the Examiner, if anything, teaches away from the invention and illustrates the need of examining each and every known or novel factor for different activities such as mobilization or particular enhancement of specific cell lineage. As such, Takayama demonstrates the need of undo experimentation in view of the prior art. Thus, both references are not relevant for the inventive step of the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 8, 11, 15, 18, 20 and 22-24 continue to be rejected under 35 USC § 103(a) as being unpatentable over Gurevitch et al taken with Bab et al. and Takayama et al. The Examiner indicates that the claims are interpreted as being drawn to various methods comprising administration of a peptide of SEQ ID NO. 1 to a subject or exposing cells to said peptide. The Examiner indicates that in some dependent claims the subjects has myeloproliferative disorder, in some cases idiopatic myelofibrosis.

The Examiner notes that Gurevitch et al. and Bab et al. (1999) do not teach treating myeloproliferative disorders or specifically increasing circulating early CD34+ stem cells or colony forming units (CFUs) in subjects with myeloproliferative disorders. The Examiner further indicates that Takayama et al. teach treating myeloproliferative disorders, including myelofibrosis, with an agent that promotes platelet and leukocyte production and reversing the damage to bone marrow caused by radiation therapy (column 12, Examples 1 and 2). Therefore, the Examiner concludes that a person of ordinary skill in the art would have had a reasonable expectation of success in treating myeloproliferative disorders, including myelofibrosis, with the OGP of Gurevitch et al. because Gurevitch et al. teach that OGP stimulates bone marrow cell production and subsequent repopulation of the immune system (Table 3 and Figure 1). Moreover, the Examiner contends that the skilled artisan would have been motivated to so modify the invention for the expected benefit of treating myelofibrosis in a patient, and therefore, according to the Examiner, the invention as a whole would have been *prime facie* obvious to a person of ordinary skill at the time the invention was made. In response to our arguments, the Examiner asserts that applicant provides a discussion of IFNγ and IL-3 as it pertains to Takayama. However, the Examiner indicated that Takayama was relied upon for teachings on the relationship between the treatment of myeloproliferative disorders and promotion of bone marrow health. The Examiner specifically indicated that there are no limitations in the claims that require "mobilization or particular enhancement of specific cell lineage," as asserted in the last paragraph of paragraph 25 in our response.

The Examiner's position in this regard is not clear to us since claim 8 is limited to CD34 positive cells (which were shown in our previous response as a very defined subtype of cells), claim 11 is dependent on claim 8, claim 15 is restricted to BFU-E, GEMM-CFU cells, and claim 18 should

have the same limitation (depend on 15). In addition to the amendments of the claims as indicated above (sections 1-5), claims 20 and 22-24 have been restricted accordingly. Clarification is requested. It is respectfully submitted that the claims have been limited as noted, to CD34 positive stem cells, and are accordingly patentable over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Double patenting

Claims 19, 26-28 and 46-48 continue to be rejected on the grounds of nonstatutory obviousness type double patenting over claim 20 of USP 5,814,610. The Examiner particularly pointed out the phrase "a subject in need thereof" in the claims, indicating that claim 20 of this patent refers to a method of treatment of various osteological conditions in "human" by administering the peptide of SEQ ID NO. 1. The Examiner indicated that all humans and animals fall within the scope of "subject in need thereof", and therefore the scope of claim 20 of the '610 patent is completely encompassed by the scope of the cited instant claims. The Examiner stated that these claims have not been restricted to a subject receiving irradiation or chemotherapy or suffering from hematological disorder, as argued in the prior response. In response, claims 19 and 26-27, are methods performed *in vitro*, and claims 28 and 46-48 have been amended to include such limitations. It is believed that the claims are free of double patenting rejections. Should allowable subject matter be indicated without the rejection having been overcome, Applicants will consider filing a terminal disclaimer.

All rejections having been addressed, it is respectfully submitted that this application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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